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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,000	05/03/2002	Tiina Nakari-Setala	0365-0529P	4534

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EXAMINER	
AFREMOVA, VERA	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 05/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,000	NAKARI-SETALA ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *10-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9 as amended and new claim 32 (3/20/2006) are under examination in the instant office action.

This application contains claims 10-31 drawn to invention nonelected with traverse in the reply filed on 8/17/2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 recites the limitation "said foaming" in the method comprising steps of modifying and culturing microorganism as intended for decreasing of foam formation. It appears that there is insufficient antecedent basis for this new limitation "said foaming" in the method of claim 1 because there is neither indication about "foaming" during the process nor there is an active step of producing "foaming" as result of culturing. Claim 32 is interpreted as drawn to the use of agitation and/or aeration means during culturing of microorganisms.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 as amended and new claim 32 remain/are rejected under 35 U.S.C. 102(b) as being anticipated by Nakari-Setala et al. (IDS reference; Eur. J. Biochem. 1997, 248: 415-423) as explained in the prior office action and for the reasons below.

Claims are directed to a method for decreasing foam formation during cultivation of microorganisms wherein the method comprises two active steps including step of modifying microorganism in a way that the microorganism does not produce one and/or two hydrophobic proteins associated with foam formation during cultivation and step of cultivating the microorganism. Some claims are further drawn to the microorganisms belonging to *Trichoderma reesei* and to hydrophobic proteins HFBI and HFB II. Some claims further encompass the use of agitation and aeration means during culturing.

The reference by Nakari-Setala et al discloses cultivating and modifying microorganism belonging to *Trichoderma reesei* under various culture conditions in a such way that the microorganism does not produce an essential amount of at least one and/or two hydrophobic proteins HFBI and HFB II. The reference by Nakari-Setala et al. teaches that expression of HFBI and HFB II is strongly induced by N and C starvation and by light (entire document including abstract) and that expression of hydrophobins is significantly reduced when microorganism is cultured in the presence of glucose (page 418, column 2, par. 2, last 3 lines). The reference discloses a method for modifying and cultivating microorganism belonging to *Trichoderma reesei* under various culture conditions in a way that the microorganism does not significantly express hydrophobins and thus, it does not significantly produce hydrophobins when cultured in the presence of glucose and/or in the dark (page 416 column 1, par. 4 and par. 7). The cited

method comprises both active step as encompassed by the presently claimed invention and, thus, it results in the same effects as the claimed method such as reduction of foam formation during cultivation of microorganism capable to produce hydrophobins. The fact that hydrophobins are associated with foam is acknowledged in the cited reference because the cited reference clearly describes that hydrophobins, when produced, are collected from foam formed in cultivation medium upon bubbling (see page 417, column 2, par. 2, last 5 lines or see page 420, column 2 par. 3). With respect to the limitation of new claim 32, the method of the cited reference comprises step of culturing microorganisms in shaken flasks (page 416, column 1, line13). The use of shaken flasks for culturing microorganisms that are potentially capable of producing hydrophobins would provide for potential foaming within the meaning of the claims.

Thus, the cited reference by Nakari-Setala et al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9 as amended and new claim 32 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakari-Setala et al. (IDS reference; Eur. J. Biochem. 1997, 248: 415-423) taken with Wosten et al. ("Interfacial self-assembly of a fungal hydrophobin into a hydrophobic rodlet layer". The Plant Cell, November 1993, Vol. 5, pages 1567-1574) and Spanu et al. ("Deletion of HCF-a, a hydrophobin gene of Cladosporium fulvum, does not affect

pathogenicity on tomato". May 1998, Vol. 52, No. 5, pages 323-334) as explained in the prior office action and for the reasons below.

Claims are directed to a method for decreasing foam formation during cultivation of microorganisms wherein the method comprises step of modifying microorganism in a way that the microorganism does not produce one and/or two hydrophobic proteins and step of cultivating the microorganism. Some claims are further drawn to the microorganisms belonging to *Trichoderma reesei* and to hydrophobic proteins HFBI and HFB II. Some claims are further drawn to genetic modification of microbial genes associated with regulation and production of hydrophobins including deletion of these genes. Some claims further encompass the use of agitation and aeration means during culturing.

The reference by Nakari-Setala et al. teaches that expression of hydrophobins, foam-associated peptides, is strongly induced by source of nutrients and light (entire document including abstract) and that expression of foam-associated hydrophobins, including HFBI and HFB II, is significantly reduced when microorganism *Trichoderma reesei* is cultured in the presence of nutrients such as glucose. Thus, the reference teaches that the fungal hydrophobin production is modified under suitable culture conditions. The cited reference also suggests modification of hydrophobin production by disruption of genes encoding for hydrophobins (page 421, column 1, par. 2) but the cited reference by Nakari-Setala et al. is lacking actual disclosure about genetic modification of microbial genes associated with regulation and production of hydrophobins.

However, Spanu et al. discloses genetic modification of microbial genes associated with regulation and production of hydrophobins such as deletion of HCF-a, a hydrophobin gene of

Cladosporium fulvum. Spanu et al. clearly teaches that deletion of hydrophobin gene reduces hydrophobicity of the fungal microorganisms but it does not affect other biological function (entire document including abstract).

The reference by Wosten et al. is relied upon to demonstrate that fungal hydrophobins are assembled on the surface of gas bubbles and they form membrane around air bubbles (see abstract). Thus, hydrophobins are foaming agent during microbial cultivation under aerated conditions by bubbling or in shaken cultures.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify microbial hydrophobin production by genetic manipulations with a reasonable expectation of success in reducing foaming during cultivation of the modified microorganisms because hydrophobins are foaming agents and/or foam-associated agents and because prior art teaches and suggests disruption of hydrophobin genes for reduction of hydrophobin production. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 3/20/2006 have been fully considered but they are not persuasive.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by Nakari-Setala et al. applicants argue that "in order for a reference to anticipate a claim, each and every

element of the claim must be disclosed either expressly or inherently in a single prior art reference and that because Nakari-setala et al. (1997) do not disclose the element of reducing a foam-associated protein, Nakari-Setala et al. do not anticipate claim 1" (paragraph bridging pages 9 and 10 of the response). This is not found true because the reference clearly recognizes, teaches and discloses the culturing conditions when hydrophobins (that are "foam-associated proteins" within the meaning of the present invention) are not detected and/or significantly reduced. For example: at page 418, column 2, par. 1-2 the reference clearly teaches that hfbI hydrophobin expression is not detected when cellulose and complex polysaccharides are used as carbon source for culturing and that addition of glucose to the culture significantly reduces hfb2 hydrophobin expression and, thus, hydrophobin production. Therefore, during culturing method as disclosed by Nakari-Setala et al the microorganism(s) are modified "in a such way that the microorganism does not produce an essential amount of at least one" and/or two hydrophobic proteins including HFBI and HFB II within the meaning of the claims. The culturing method as disclosed by Nakari-Setala et al, (for example: at page 416, par. 2) comprises the use of cellulose and complex polysaccharides as well as addition of glucoses in a medium for culturing microorganisms wherein the use of these carbon sources causes modification of microorganisms that are capable to produce hydrophobins "in a such way" that the microorganism do not express hydrophobins and, therefore, do not produce hydrophobins.

Applicants appear to argue that the cited reference does not disclose "any data at all regarding whether or not HFBI (hydrophobin) is present in an agitated and aerated culture medium" (response page 9, par. 2). However, even regardless whether or not this is true, the

claimed method does not require steps of detecting, recovering and/or measuring any amounts of proteins associated with foam formation including hydrophobins that would be produced or not.

Applicants appear to argue that the cited reference does not recognize that hydrophobins including HFBII are associated with the problem of foaming (response page 8, par. 2). The fact that hydrophobin HFBII is associated with foam is acknowledged in the cited reference because the cited reference clearly describes that hydrophobins, when produced, are collected from foam formed in cultivation medium upon bubbling (see page 417, column 2, par. 2, last 5 lines or see page 420, column 2 par. 3). Moreover, the cited reference also discloses that hydrophobins cause technical problems encountered in large fermentor cultivations including problems of overfoaming (page 421, col. 2, par. 4).

With regard to the claim rejection under 35 U.S.C. 103 applicants appear to argue that the cited references are nonanalogous art. In response to applicant's argument it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the reference by Nakari-Setala et al. teaches culture conditions that cause reduction in hydrophobin expression and the cited reference also suggests modification of hydrophobin production by disruption of genes encoding for hydrophobins (page 421, column 1, par. 2). The other cited references demonstrate that disruption of genes encoding for hydrophobins and/or deletion of these genes has been known and practiced in the prior art (Spanu et al.) and that hydrophobins are foam-associated agents

during microbial cultivation under aerated conditions by bubbling or in shaken cultures (Wosten et al.). Thus, the cited references are in the same field of endeavor and they seek to solve the same problems as the instant application and claims and one of skill in the art is free to select and combine knowledge available in the prior art. One of skill in the art would have been motivated to modify microorganisms in order to reduce amounts of microbial hydrophobin production for the expected benefits in reducing foam formation since hydrophobins are foam-associated compounds and since foaming is a technical problem in large fermentor cultivations as it is recognized by the cited prior art.

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1651

May 24, 2006

VERA AFREMOVA

PRIMARY EXAMINER